REMARKS

A. State of Claims

Claims 2-4, 6-35 and 37-41 and 52-55 are currently pending. New claims 56-61 are added by amendment. Support for the new claims can be found at least on page 7, lines 5-14 and 26-31, and page 33, line 23 to page 34, line 20 of the specification. Claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 are rejected under 35 U.S.C. 112, first paragraph, as not being enabled for the full scope of the claimed invention. Claims 2-4, 6, 8, 10, 15, 20, 23, 30, 31, 32, 33-35, and 37-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Claims 7, 11-14,6-19,21,22,24-29, and 52-55 are objected to as being dependant upon a rejected base claim. Claims 2, 7, 9, 20, 32 and 35 have been amended to further clarify the claims.

B. Rejection based on 35 U.S.C. 112, first paragraph

The Action rejects claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 under 35 U.S.C. 112, first paragraph, as not being enabled for the full scope of the claimed invention, in particular methods of synthesizing EC conjugates of anticancer agents, tumor markers, folate receptor targeting ligands, tumor apoptotic cell targeting ligands, tumor hypoxia targeting ligands, or agents that mimic glucose. Applicants respectfully traverse.

35 U.S.C. 112, first paragraph, states in part that the specification shall contain a written description of the manner and process of making and using the claimed invention in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the same. It is permissible for some experimentation to be required to practice the claimed invention, so long as it is not undue. *Atlas Powder Co. v. E.I. Dupont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed.Cir.1984). Applicants also note that "[a]s long as the specification discloses at least one method for making and using

the claimed invention that bears a reasonable correlation to the entire scope of the claims, then the enablement requirement is satisfied." MPEP 2164.01(b) citing *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

1. No factual basis is provided to support rejection of claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 under 35 U.S.C. 112, first paragraph

First, Applicants observe that the Action provides no factual basis to rebut the teachings of the specification or support the premise that one skilled in the art would have to undertake undue experimentation to "obtain a tissue specific ligand, wherein the tissue specific ligand is an anti-cancer agent, a tumor marker, a folate receptor targeting ligand, a tumor apoptotic cell targeting ligand, a tumor hypoxia targeting ligand, or an agent that mimics glucose...admixing said ligand with ethylenediceysteine (EC) to obtain an EC-tissue specific ligand derivative; and...admixing said EC-tissue specific ligand derivative with a radionuclide and a reducing agent to obtain a radionuclide labeled EC-tissue specific ligand derivative, wherein the EC forms an N_2S_2 chelate with the radionuclide." The Examiner is referred specifically to MPEP §2164.04, which provides that it is the Examiner's burden to come forward with factual evidence that would raise a "doubt as to the objective truth of the statements" contained in the application regarding enablement. See, *e.g.*, In re Marzocchi, 169 U.S.P.Q. 367, 370 (CCPA 1971). This has not been done here.

2. Undue experimentation is not needed to practice the invention of claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41

In light of the teachings of the specification and the level of skill in the art, undue experimentation is *not needed* for one of ordinary skill in the art to synthesize a tissue specific ligand-EC conjugate (EC-ligand conjugate) as claimed. Factors to be considered include (1) the nature of the invention, (2) state of the prior art (3) level of one of ordinary skill in the art, (4) level of unpredictability in the art, (5) amount of direction an guidance provided by the inventor (6) existence of working examples (7) breadth of the claims and (8) the quantity of

experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988).

a. The art related to the claimed invention was well developed and skill in the art was high

As stated in the Action on page 4, the nature of the invention is directed to methods of synthesizing EC-tissue specific ligand complexes. The state of the art is one in which radiolabeling of N_2S_2 chelates was known, as exemplified by the Anderson *et al.* 1995, citation on page 5 of the Action. Also known in the art were synthetic methods for conjugating imaging agents to targeting agents based on the available functional groups of the targeting agent, *see* U.S. Patent 5,517,993 column 7, line 53 to column 8, line 26. Thus, one of ordinary skill in the art of imaging agent conjugation possessed a high level of skill in conjugating imaging agents to targeting agents.

b. The specification provides sufficient guidance to one of skill in the art for the purpose of selecting a targeting agent

One of ordinary skill in the art, in light of the specification, could have readily selected a targeting agent to be used in the claimed methods for synthesizing an EC-tissue specific ligand conjugate. Applicants provide guidance to the skilled artisan by means of a number of examples illustrating the coupling of EC to a representative number of tissue specific ligands. The tissue specific ligands described in the specification are representative of the various classes of tissue specific agents, including anti-cancer agents (specification, page 5, line 16-18), tumor markers (specification, page 5, line 18-21), folate receptor targeting ligands (specification, page 5 line 23), tumor apoptotic and tumor hypoxia cell targeting ligands (specification, page 5, line 24-25), and agents that mimic glucose (specification, page 5, Line 29 to page 6, line 2).

In further support, Applicants reference the scientific literature to demonstrate that one of skill in the art, based on the teachings of the specification, would be able to readily identify and select a tissue specific ligand of the invention. There are a variety of methods known in the art

for the identification of ligands and the characterization of the identified ligand as an anticancer agent (Yamori *et al.*, 1999 – *in vitro* and *in vivo* growth inhibition assays), a tumor marker (Hibi *et al.*, 1999; Becker *et al.*, 1999 – northern blotting western blotting and immunohistochemisttry), a folate receptor targeting ligand (Sudimack and Lee, 2000 – radiolabeled ligand binding), a tumor apoptotic cell targeting ligand (Takamizawa *et al.*, 2000 – RNase protection and western blotting assays), a tumor hypoxia targeting ligand (Garayoa *et al.*, 2000 – northern blotting, immunohistochemistry, and luciferase reporter assays), or an agent that mimics glucose (Kanazawa *et al.*, 1997 – *in vivo* distribution studies and NMR analysis). Specifically, the specification identifies various anticancer agents in Table 2 on pages 34-41. In addition, Yamori *et al.*, on page 4043, describe methods that exemplify the identification of anticancer agents by analysis of cell growth inhibition and antitumor activity against nude mouse xenografts. Hibi *et al.* describe using northern blot, western blot, and immunohistochemical analysis of various cancer cells and non-cancer cells to identify the tumor marker PGP9.5. Becker *et al.* describe the use of a monoclonal antibody as a tumor marker to identify tumor cells expressing an aberrant form of E-cadherin.

Detection of folate receptor targeting is exemplified in Sudimack and Lee (2000) on page 151 to 152 where localization of a folate receptor ligand is accomplished by *in vitro* and *in vivo* radiolabeled ligand studies. An example of tumor apoptotic cell targeting ligand identification is provided in Takamizawa *et al.* where the expression of proapoptotic proteins is assayed by RNase protection and western blotting assays. A tumor hypoxia targeting ligand may be identified by using northern blotting, immunohistochemistry, and luciferase reporter assays in conjunction with hypoxic cell culture as described in Garayoa *et al.*. Kanazawa *et al.* identify the tumor localization of glucose mimics or analogs by using *in vivo* distribution studies and NMR analysis. Any of these methods in combination with the guidance provided may be used for identifying a tissue specific agent of the invention.

c. The specification provides sufficient guidance to one of skill in the art for purposes of identifying the necessary conjugation chemistry

If the Examiner's concerns are related to the presence of appropriate functional groups on the selected tissue specific ligand, the specification provides a detailed description of the conjugation chemistry. Applicants refer the Examiner to at least page 6, lines 4-18; page 22, line 18 to page 23, line 23; FIG. 1-3, 7, 8A, 16, 21, 36, 49, 54, and 59 for a detailed description of the chemistry and functional groups underlying the conjugation of EC to representative tissue specific ligands. Of particular interest is Table 1 on page 23 of the specification that illustrates exemplary linkers that can be used to conjugate EC to a variety of functional groups. One of skill in the art is capable of identifying a functional group(s) of a tissue specific ligand that is useful for the synthetic methods claimed.

d. Routine imaging and distribution studies

Once an EC-conjugate is synthesized according to the present invention, one of skill can readily confirm its imaging capabilities through the application of imaging studies such as the cellular uptake and distribution studies exemplified throughout the examples section, pages 32-68 of the specification. In particular, cellular uptake studies are exemplified throughout the examples section and in FIGs. 46-48, 55-58, 69-73, and 76-80; whereas distribution studies are exemplified throughout the examples section and in FIGs. 6, 11, 12, 14, 15, 17-20, 25, 26, 28-35, 37, 81-86. No undue experimentation is needed to carry out the teachings of the specification and perform the claimed methods for synthesizing imaging conjugates.

Claims may be rejected if persons skilled in the art must resort to elaborate, considerable, or unreasonable experimentation in order to practice an invention. In light of the foregoing, such undue experimentation is *not required* to practice the methods for synthesizing an EC-tissue specific ligand conjugate. Applicants respectfully request withdrawal of the rejection.

C. Rejections based on 35 U.S.C. 112, second paragraph

The Action rejects claims 2-4, 6, 8, 10, 15, 20, 23, 30, 31, 32, 33-35, and 37-41 as being indefinite. In particular the Action states that one of ordinary skill in the art would not be able to ascertain what is encompassed in the claims. Applicants respectfully traverse.

1. Claim 9 has been clarified by amendment

Claim 9 has been rejected as unclear based on the recitation of anitbody or antisense and that these ligands are not encompassed by the claims from which the claims depend. In addition, the Action states that the independent claims were amended to remove "antibody" as a tissue specific ligand. Applicants have reviewed the record and have not identified any amendment that removes antibody from the list of tissue specific ligands. "Antibody" and antisense are included in the tumor marker class of tissue specific ligands as stated in the specification on at least page 5, line 21. Applicants respectfully request withdrawal of the rejection of claim 9.

2. Claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 are clear and definite

The Action rejects claims 2-4, 6, 8, 10, 15, 23, 30, 31, 33-35, and 37-41 based on the premise that the phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are unlimited. Applicants respectfully traverse.

The phrases "anticancer agent," "tumor marker," "folate receptor targeting ligand," "tumor apoptotic cell targeting ligand," "tumor hypoxia targeting ligand," and "an agent that mimics glucose" are terms used to refer to specific classes of targeting ligands. Each class of targeting ligand, when taken in light of the description provided in the specification, is readily discernable to one of ordinary skill in the art. Applicant refers to the preceding discussion related to ability of one of skill in the art to readily identify or obtain tissue specific ligands as described in the specification and in the art. Applicants respectfully request the withdrawal of the rejection.

3. Claim 20 has been clarified by amendment

Claim 20 has been rejected as being ambiguous due to a typographical error. Claim 20 has been amended to read 99mTc-EC-metronidazole, thus rendering the rejection of the claim moot.

4. Claim 32 has been clarified by amendment

Claim 32 is rejected under 35 U.S.C. 112, second paragraph as being indefinite due to the recitation of estradiol, octreotide, or VIP. Claim 32 has been amended herein for clarity, the recitation of octreotide is maintained based on its identification as an anticancer agent in Table 2 on page 36 in the row labeled islet cell. The rejection of claim 32 is rendered moot.

D. Objection of claims 7, 11-14, 6-19, 21, 22, 24-29, and 52-55

The action objects to claims 7, 11-14, 6-19, 21, 22, 24-29, and 52-55 as being dependant upon a rejected base claim. Based on the foregoing the base claims are in condition for allowance, thus the objection of claims 7, 11-14, 6-19, 21, 22, 24-29, and 52-55 is moot. The withdrawal of the rejection is respectfully requested.

E. Conclusions

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below at (512) 536-3055.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

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Date: March 29, 2004